Reviewer's report

Title: Expression of nerve growth factor and heme oxygenase-1 predict poor survival of breast carcinoma patients

Version: 1 Date: 15 July 2013

Reviewer: Gary Tse

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This is an interesting study on NGF and HO1 expression in a series of breast cancer.

Major Compulsory Revisions

1. Please confirm the TM tissue core size is 3mm in diameter per core. It is well documented that intratumoral heterogeneity existed in breast cancer. As only a single core was selected from each case, there could be potential selection bias.

2. The 30% cutoff criteria were used previously for other markers and in other tumors. It may not necessarily applicable for HO-1 and NGF as well as for markers in breast cancers. What is the basis for this criteria in the current study?

3. Some details (including mean/ median/ range of follow up time, no of cases of breast cancer specific death, number of cases of relapse, etc) on follow up data are missing.

4. The author suggested the co-expression of NGF and HO-1 has the worst survival and could have synergistic effect. However, it is not very convincing. The survival curve of NGF positive is very similar to that of NGF+HO-1+. In their analysis, cases expressed either HO-1 and NGF was grouped together. In that group (either HO-1/NGF pos), majority was HO-1 positive (34/47). The difference in survival may just reflect the difference due to HO-1 and NGF. Though a higher HR for NGF+HO-1+ than NGF positive, the former is compared to the double negative cases while the latter is referenced to NGF negative cases. Therefore, cases with expression of a single marker should be analyzed as two separate groups.

5. 110/145 cases were having both chemotherapy and hormonal therapy. Less than 20 cases have received only single therapy. It is not very meaningful for the additional analysis based on different therapies. The current data mainly based on patients received combined treatments and did not support the discussion on the relationship of NGF and chemoresistance.

6. The role of NGF on breast cancers is dependent on its receptors. There are reports in the literature of TrkA/NFGR expression in breast cancer (e.g. J Clin Pathol 2013;66:4 291-296). It would be of interest to the readers if the results of the current study and its receptor expression are discussed.
**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

'I declare that I have no competing interests'